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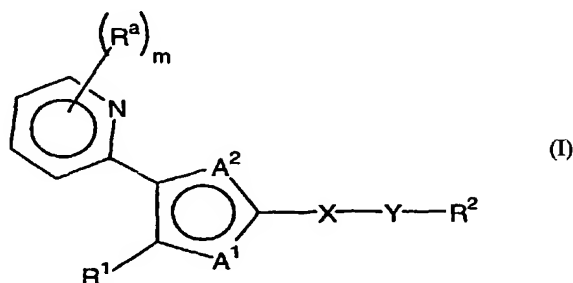
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(54) Title: TRI-SUBSTITUTED HETEROARYLS AND METHODS OF MAKING AND USING THE SAME



(57) Abstract: Compounds of formula (I) possess unexpectedly high affinity for Alk 5 and/or Alk 4, and can be useful as antagonists thereof for preventing and/or treating numerous diseases, including fibrotic disorders. In one embodiment, the invention features a compound of the general formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/10440

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : Please See Extra Sheet.
US CL : Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/249, 259, 318, 340, 341, 342; 544/253, 353 ; 546/193, 256, 268.4, 271.4, 272.4, 272.7

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-structure
EAST/WEST-subclasses

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	DATABASE CASPLUS on STN (COLUMBUS, OH, USA), No. 137:93761, 'Preparation of 2-imidazolyl-1,3-dioxane-5-carboxamides and analogs as ALK-5 receptor inhibitors', Gaster et al. PCT application, July 2002. See RN 442517-17-1 and RN 442517-19-3.	1, 2, 10, 11, 13, 18, 19, 34, 35
X	DATABASE CAPLUS on STN (COLUMBUS, OH, USA), No. 132:308351, 'Preparation of 5,7-disubstituted-4-aminopyrido- [2,3-d]pyrimidines as adenosine kinase inhibitors' Bhagwat et al. PCT application 2000, see RN 165106-96-5.	1, 2, 10, 11, 13, 15-19

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/10440

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS on STN (COLUMBUS, OH, USA) NO. 118:254935, 'Preparation of 4-(2-pyridyl)thiazole and 3-(2-pyridyl)1,2,4-thiadiazole derivatives as agrochemical and horticultural fungicides'. Kasahar et al. 1992, see RN 147110-22-3.	1, 2, 10, 11, 13, 18, 19
X	DATABASE CAPLUS on STN(COLUMBUS, OH, USA), No. 130:139196, 'Total synthesis of endothelin-converting enzyme antagonist WS75624 B' Huang et al. Tetrahedron Letters, Vol. 39, No. 51, pages 9335-9338 (1998), see RN 220089-80-5.	1, 2, 11, 13, 18, 19
X	DATABASE CASPLUS on STN (COLUMBUS, OH, USA), No. 87:135172, 'Reaction of 5-chloropyridin-2-yl-thioureas with phenacyl bromides:a new thiazole synthesis. x-ray crystal structure of 5-(5-chloropyridin-2-yl)-2-diethylamino- 4-phenylthiazole' LeCount et al. J. of Chem. Society, chem commun. 1997, Vol. 8, pages.282-283. See RN 64228-09-7.	1, 2, 10, 11, 13, 18, 19

INTERNATIONAL SEARCH REPORT

Inter: 1 application No.
PCT/US03/10440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PC 3/10440

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (7):

IPC7: A61K 31/36, 31/395, 31/41, 31/435, 31/517; C07D 401/04, 401/14, 405/04, 405/14, 409/04, 409/14

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/249, 259, 318, 340, 341, 342; 544/253, 353 ; 546/193, 256, 268.4, 271.4, 272.4, 272.7

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-20, 26-49, wherein X is monocyclic cycloalkyl, drawn to compounds, compositions and method using material which has at least three ring core including a monocyclic cycloalkyl.

Group II, claims 1-20, 26-49, wherein X is bicyclic cycloalkyl, drawn to compounds, compositions and method of using material has at least three ring core with one being bicycloalkyl.

Group III, claims 1-49, wherein X is heteroalkyl, drawn to compounds, compositions and method of using material has at least three monoheterocyclic ring core.

Group IV, claims 1-20, 26-49, wherein X is bicyclic heterocycle, drawn to compounds, compositions and method of using material has at least three heterocycle ring core with one being bicyclic heteroalkyl.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: under Administrative Instruction Annex B, regarding Markush practice, it was stated that in paragraph (f)(i)(B)(2)v, "When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner".

In the instant case, the compounds wherein X is monocyclic cycloalkyl is not novel (see CA 136:325539 RN 412351-70-3) and does not share the same utility. Therefore, unity of invention is lacking since the core structure must include the X ring each of which is a separate class of compounds.